REMARKS

The above-captioned application claims priority under 35 U.S.C. § 119(e) to Application Serial No. 60/415,216, which was filed September 30, 2002.

Claims 1-65 are pending in this application. Claims 1-19 and 27-29 are currently under consideration, while claims 20-26 and 30-65 have been withdrawn from consideration. Claims 1-19 and 27-29 stand rejected. Claims 1 and 27-29 have been cancelled. Claims 2-12, 16, 30, 31, 44, 46, 50, 51, 56, 58 and 59 have been amended.

Election/Restriction

The examiner stated that applicant must affirm the provisional election of Flp recombinase as the elected recombinase activity of the rec element, as per the species election requirement.

Applicant hereby affirms the provisional election of Flp recombinase.

Drawings

The drawings stand objected to for failing to comply with 37 C.F.R. § 1.84(p)(5). Specifically, the examiner stated that Figure 10 is not mentioned in the description.

The specification has been amended to include reference to Figure 10. Specifically, applicant has amended paragraph [201] to refer to Figure 10. Paragraph [201] clearly refers to Figure 10 because it makes reference to four integration cassettes that can be integrated into a cell, CE 5.0-8.0, which are depicted in Figure 10. The additional amendments to paragraph [201] merely correct obvious grammatical errors. Accordingly, no new matter has been added by the amendments to paragraph [201]. In

addition, applicant has added paragraph [40.1] to briefly describe Figure 10. This description was taken from paragraph [201] and elsewhere in the specification. Therefore, no new matter has been added by the addition of paragraph [40.1]. Accordingly, withdrawal of the objection to the drawings is respectfully requested.

Claim Objection

Claim 8 has been objected to for not reciting the word "system".

Claim 8 has been amended accordingly. Withdrawal of the objection to claim 8 is respectfully requested.

Rejection under 35 U.S.C. § 112, 2nd paragraph

Claims 7, 10, 12, 16 and 28 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite. Specifically, the examiner stated that the metes and bounds of the term "TAG sequence" are unclear because it can either be interpreted literally as the nucleic acid sequence "TAG", which could potentially be utilized as a stop codon, or a sequence encoding a tag.

In order to expedite prosecution of the instant application, applicant has amended claims 7, 10, 12 and 16 to recite a "tag" rather than a "TAG sequence". Support for the amendment can be found in the specification on pages 28 (line 2 of paragraph 108), 35 & 36 (paragraphs 130 and 131), and 58 (paragraph 213). Accordingly, no new matter has been added. Claim 28 has been cancelled.

Applicant believes he has addressed the examiner's concerns because the term "tag" should not be interpreted literally as a stop codon. In addition, applicant believes

that a person having ordinary skill in the art would understand the term "tag" when read in light of the specification. Therefore, it is applicant's belief that the scope of claims 7, 10, 12 and 16 are clear. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, 2nd paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1, 4, 5 and 27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bode *et al.* (EP 0 939 120 A1).

Applicant has cancelled independent claims 1 and 27. Dependent claims 4 and 5 have been amended to depend from claim 11. Therefore, applicant believes that this rejection has been rendered moot. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 in view of Bode *et al.* is respectfully requested.

Claims 1, 4, 5, 8 and 27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Seibler *et al.*, Biochemistry, vol. 36, pp. 1740-1747 (1997).

Applicant has cancelled independent claims 1 and 27. Dependent claims 4, 5 and 8 have been amended to depend from claim 11. Therefore, applicant believes that this rejection has been rendered moot. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 in view of Seibler *et al.* is respectfully requested.

Claims 1-3, 5, 8 and 27 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Ow, U.S. Patent Application Publication No. 2002/0123145.

Applicant has cancelled independent claims 1 and 27. Dependent claims 2, 3, 5 and 8 have been amended to depend from claim 11. Therefore, applicant believes that this rejection has been rendered moot. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 in view of Ow is respectfully requested.

Claims 27-29 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051.

Applicant has cancelled claims 27-29. Therefore, this rejection has been rendered moot. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 in view of Cheo *et al.* is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1, 4-19 and 27-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cheo *et al.* ("Cheo") in view of Siebler *et al* ("Siebler"). Claims 1 and 27-29 have been cancelled. Therefore, the rejection with respect to those claims is rendered moot. Claims 4-10 have been amended to depend from claim 11. Claims 12-19 also depend from claim 11. In light of the following remarks, applicant respectfully traverses the above rejection and requests reconsideration of claims 4-19.

Amended claim 11, and the claims that depend therefrom, recite a cellular expression system comprising a first integration cassette, a first target cassette, a second integration cassette, a second target cassette, and at least one rec element.

Cheo, the primary reference relied on by the examiner, relates to materials and methods for joining or combining two or more nucleic acid molecules containing

recombination sites (paragraphs 3, 43, 46, 51 and 73). In addition to joining multiple nucleic acids, Cheo also relates to replacing one or more nucleic acids in a product molecule by recombination with another molecule (paragraph 75). Cheo calls this method recombinational cloning. Paragraphs 40-42 of Cheo describe recombinational cloning. Briefly, recombinational cloning utilizes vectors that contain at least one recombination site to clone desired nucleic acid molecules. Nucleic acid fragments flanked by recombination sites are cloned and subcloned by replacing a selectable marker on the recipient plasmid molecule, sometimes termed the Destination Vector.

Contrary to the examiner's assertion, Cheo does not teach the cellular expression system of claim 11. Firstly, Cheo does not teach an integration cassette. The examiner, on page 10 of the Office Action states that Cheo teaches a vector comprising two recombination sites flanking promoters and selectable markers. Such a design is not consistent with the cellular expression system and integration cassettes of the present invention. Rather, the cellular expression system of the present invention comprises integration cassettes wherein the promoter is located outside the recombination site. Therefore, as stated in paragraph 104 of the present application, once a transformant comprising an integration cassette that supports a desired level of expression has been isolated, the exchangeable reporter segment can be replaced with the exchangeable target segment such that the target segment will be transcribed at the same rate that the reporter was transcribed. By allowing the expression level of the randomly integrated integration cassette to be evaluated prior to substitution with, and production of, a desired protein product, the integration cassettes of the present invention allow for the rapid development of stable expression system displaying desirable transcriptional levels.

In addition, even though the Cheo vectors may contain sequences, such as transposable elements, that allow for integration into eukaryotic chromosomes, the Cheo vectors randomly integrate into the genome. This approach leads to a number of problems due to the random nature of the integration event. First, some of the locations where recombinant genes are inserted are incapable of supporting transcriptional events. Even if the genes are inserted into a location that allows for transcription, this random integration method offers no control over the transcriptional fate of the integrated nucleic acid. Consequently, wide variations in the expression level of the integrated nucleic acid can occur. Furthermore, random insertion into the cellular genetic material requires several rounds of selection and clonal expansion to produce an acceptable expression system. To produce expression systems for multi-subunit complexes by this random process increases the complexity of acquiring the expression system by several orders of magnitude.

Again, such a design is not consistent with the cellular expression system and integration cassettes of the present invention. As stated in paragraphs 84 and 85 of the present specification, the integration cassettes are inserted into genomic sites by non-homologous recombination such that cell populations that support optimal expression features are established. The expression system permits the exchange of the coding regions while leaving the remainder of the expression system, including the promoter, in place. This approach is advantageous because it eliminates the need for repetitive rounds of selection and clonal expansion when a new gene is to be swapped into the system. Instead, a prescreened cellular expression system of the present invention can be selected,

and the gene of interest swapped into the system. This places the gene of interest under the control of a known promoter supporting a known level of expression.

Furthermore, Cheo does not teach the combination of the integration cassettes, target cassettes and rec element that comprise the cellular expression system of claim 11. Contrary to the examiner's assertion, paragraph 152 of Cheo (I believe the examiner is referring to paragraph 152 of the published application, as that is the section quoted in the Office Action) merely teaches the recombination of two nucleic acids into one or more vectors. Figures 6 and 7 of Cheo teach this same concept. Paragraph 75 of Cheo teaches the replacement of one or more nucleic acids by recombination with a different nucleic acid. For the reasons stated above, none of the cited paragraphs or drawings teach the combination of integration cassettes of the cellular expression system that permit the exchange of their coding regions while leaving the remainder of the system intact. In addition, Cheo does not teach a rec element encoding at least one recombinase activity.

The additional reference cited by the examiner, either alone or in combination, also fails to disclose or suggest the claimed cellular expression system. Seibler relates to double-reciprocal crossover that is mediated by FLP-Recombinase, *i.e.*, a recombinase-mediated cassette exchange reaction. Even though Seibler discloses a recombinase plasmid, such a teaching does not cure the deficiencies of Cheo. As discussed above, Cheo does not teach an integration cassette, and certainly does not teach a combination of integration cassettes to form the cellular expression system of claim 11.

For the reasons stated above, the combination of Cheo and Seibler do not teach or suggest the cellular expression system of amended claim 11. Accordingly, withdrawal of

the rejection of claims 1, 4-19 and 27-29 under 35 U.S.C. § 103(a) over those references is respectfully requested.

Claims 1, 4-19 and 27-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cheo *et al.* in view of Cox *et al.* Claims 1 and 27-29 have been cancelled. Therefore, the rejection with respect to those claims is rendered moot. Claims 4-10 have been amended to depend from claim 11. Claims 12-19 also depend from claim 11.

In light of the above remarks, applicant respectfully submits that Cheo does not teach the cellular expression system of claim 11.

The additional reference cited by the examiner, either alone or in combination, also fails to disclose or suggest the claimed cellular expression system. Cox relates to chromosomal targeting in bacteria using FLP recombinase. However, such a teaching does not cure the deficiencies of Cheo. As discussed above, Cheo does not teach an integration cassette, and certainly does not teach a combination of integration cassettes to form the cellular expression system of claim 11.

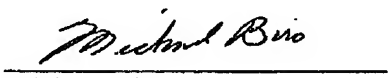
For the reasons stated above, the combination of Cheo and Cox do not teach or suggest the cellular expression system of amended claim 11. Accordingly, withdrawal of the rejection of claims 1, 4-19 and 27-29 under 35 U.S.C. § 103(a) over those references is respectfully requested.

CONCLUSION

Applicant submits that claims 2-19 of the present invention recite a novel and non-obvious cellular expression system, as the cited references do not teach or suggest the claimed system. Applicant also submits that the claims are definite. In view of the foregoing, applicant respectfully submits that the subject application is in condition for allowance. Accordingly, reconsideration of the rejections and allowance of the claims are earnestly solicited.

If the undersigned can be of assistance to the examiner in addressing issues to advance the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



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